IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IOVATE HEALTH SCIENCES U.S.A., INC., IOVATE HEALTH SCIENCES INTERNATIONAL, INC., IOVATE T & P, INC., FLAMMA SpA, and USE TECHNO CORPORATION, Plaintiffs, v. WELLNX LIFE SCIENCES INC (d/b/a NV Inc.), NXCARE INC., NXLABS INC., SLIMQUICK LABORATORIES, BIOGENETIX, DEREK WOODGATE, and BRADLEY WOODGATE, Defendants.	)	Civil Action No. _____ JURY TRIAL DEMANDED

COMPLAINT

Plaintiffs Iovate Health Sciences U.S.A., Inc. ("Iovate U.S.A."), Iovate Health Sciences International, Inc. ("Iovate International"), Iovate T & P, Inc. ("Iovate T & P") (collectively "Iovate"), Flamma SpA ("Flamma") and Use Techno Corporation ("UTC") (collectively "Plaintiffs"), hereby allege for their Complaint against WellNx Life Sciences Inc. ("WellNx") (d/b/a NV Inc.), NxCare Inc. ("NxCare"), NxLabs Inc. ("NxLabs"), Slimquick Laboratories ("Slimquick"), Biogenetix, Derek Woodgate and Bradley Woodgate (collectively "Defendants"), on personal knowledge as to their own activities and on information and belief as to all other matters, as follows:

PARTIES

1. Iovate U.S.A. is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 3880 Jeffrey Boulevard, Blasdell, New York, NY, 14129.

2. Iovate International is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at 5100 Spectrum Way, Mississauga, ON, Canada, L4W 5S2.

3. Iovate T & P is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at 5100 Spectrum Way, Mississauga, ON, Canada, L4W 5S2.

4. Flamma is a corporation organized and existing under the laws of Italy, with its principal place of business at Via Bedeschi 22-24040 Chignolo d'Isola, Italy.

5. UTC is a company with its principal place of business at 4-27 Sasaoshinmachi, Fukuchiyama-shi, Kyoto, Japan 620-0055.

6. Upon information and belief, Defendant WellNx is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9, and/or 218 Silvercreek Parkway, Guelph, ON, Canada.

7. Upon information and belief, Defendant NxCare is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

8. Upon information and belief, Defendant NxLabs is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

9. Upon information and belief, Defendant Slimquick is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

10. Upon information and belief, Defendant Biogenetix is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

11. Upon information and belief, Defendants Derek Woodgate and Bradley Woodgate are individuals and the founders of WellNx (and its predecessor entities), NxCare, NxLabs, Slimquick, Biogenetix, and are officers, shareholders, and/or directors of WellNx, NxCare, NxLabs, Slimquick, Biogenetix, and personally direct and control the activities herein complained.

12. Upon information and belief, Defendant Derek Woodgate resides at 1594 Waldie Avenue, Milton, ON, Canada, L9T 5K8.

13. Upon information and belief, Defendant Bradley Woodgate resides at 803-373 Front Street West, Toronto, ON, Canada, M5V-3R7.

JURISDICTION AND VENUE

14. This is an action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code. Accordingly, this Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

15. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1331, 1391(b), 1391(d) and 1400.

16. Upon information and belief, Defendant WellNx maintains an office at 1201 N. Orange Street, Suite 741, Wilmington, DE, 19801.

17. Upon information and belief, Defendant NxCare maintains an office at 874 Walker Rd., Dover, DE 19904.

GENERAL ALLEGATIONS

18. On October 26, 1999, United States Patent No. 5,973,199 ("the '199 patent"), titled "Hydrosoluble Organic Salts of Creatine," was duly and legally issued by the United States Patent and Trademark Office. A true and correct copy of the '199 patent is attached as Exhibit A of this Complaint.

19. Flamma is the owner and assignee of the '199 patent.

20. Iovate Health Sciences U.S.A., Inc. is the exclusive licensee of the '199 patent.

21. On April 6, 2004, United States Patent No. 6,716,459 ("the '459 patent"), titled "Composition for Inhibiting Increase of Blood Sugar Level or Lowering Blood Sugar Level," was duly issued by the United States Patent and Trademark Office. A true and correct copy of the '459 patent is attached as Exhibit B of this Complaint.

22. UTC granted an exclusive license to Iovate International, and its affiliates, for the entire scope of the claims of the '459 patent.

23. On October 19, 1999, United States Patent No. 5,968,900 ("the '900 patent"), titled "Increasing Creatine and Glycogen Concentration in Muscle," was duly issued by the United States Patent and Trademark Office. A true and correct copy of the '900 patent is attached as Exhibit C of this Complaint.

24. Iovate T & P is the owner of all rights, title and interest in and to the '900 patent.

25. Upon information and belief, Defendants have made, used, offered for sale, sold and/or imported nutritional supplements, including Slimage, Slimquick Night, Vaso, Vaso XP,

Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, Aminovol, Pump System, and/or Creatine-D^2T throughout the U.S. and in this judicial district.

26. The product label for the Slimage product lists "Lagerstroemia Speciosa (leaf) (standardized for 5% corosolic acid)".

27. The product label for the Slimquick Night product lists "Banabo extract (Lagerstroemia Speciosa) (leaf) Standardized for 5% Corosolic Acid)".

28. The supplement facts for the Hypergrowth product lists "Corosolic acid" as an ingredient.

29. The supplement facts for the Aminovol product lists "Corosolic acid" as an ingredient.

30. The product label for Creatine-D^2T lists 4000 mg of Creatine derivatives (Creatine Ethyl Ester, Creatine AKG, and Creatine Decanoate) per serving, and an "Insulin Signaling Complex".

31. The supplement information for Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine), and "InsuTech." "Each serving of Hypergrowth delivers 10g of CreaPlex3 . . . for maximum creatine absorption and retention."

FIRST CAUSE OF ACTION
(Infringement of the '199 Patent)

32. Plaintiffs repeat and re-allege the allegations of paragraphs 1-31 of the Complaint as if set forth herein.

33. By their actions, Defendants have infringed and are infringing the '199 patent.

34. Upon information and belief, the infringement by Defendants has been and continues to be willful.

35. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

SECOND CAUSE OF ACTION
(Infringement of the '459 Patent)

36. Plaintiffs repeat and re-allege the allegations of paragraphs 1-35 of the Complaint as if set forth herein.

37. By their actions, Defendants have infringed and are infringing the '459 patent.

38. Upon information and belief, the infringement by Defendants has been and continues to be willful.

39. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

THIRD CAUSE OF ACTION
(Infringement of the '900 Patent)

40. Plaintiffs repeat and re-allege the allegations of paragraphs 1-39 of the Complaint as if set forth herein.

41. By their actions, Defendants infringed and are infringing the '900 patent.

42. Upon information and belief, the infringement by Defendants has been and continues to be willful.

43. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for entry of judgment against each Defendant as follows:

A. The Defendants infringe the '199, '459, and '900 patents by their making, using, offering for sale, selling and/or importing nutritional supplements, including Vaso and/or Vaso

XP, Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, Pump System, Slimage, Slimquick Night, Aminovol and Creatine-D^2T;

B. That Defendants' infringement of the '199, '459, and '900 patents is willful;

C. That Defendants, their officers, directors, affiliates, agents, servants, employees and attorneys, and all those persons acting in privity or in concert with any of them, be preliminarily and permanently enjoining from infringement of the '199, '459, and '900 patents;

D. That Plaintiffs be awarded their damages for infringement of the '199, '459, and '900 patents, and that the damages be trebled;

E. That this case be declared to be exceptional in favor of Plaintiffs under 35 U.S.C. § 285, and that Plaintiffs be awarded their costs, attorneys' fees, and other expenses incurred in connection with this action; and

F. That Plaintiffs be awarded such other and further relief as may be appropriate.

DEMAND FOR JURY TRIAL

Plaintiffs demand a trial by jury.

Dated: May 24, 2007

Respectfully submitted,

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US005973199A

United States Patent [19]

Negrisoli et al.

[11] **Patent Number: 5,973,199**

[45] **Date of Patent: *Oct. 26, 1999**

[54] **HYDROSOLUBLE ORGANIC SALTS OF CREATINE**

[75] Inventors: **Gianpaolo Negrisoli**; **Lucno Del Corona**, both of Bergamo, Italy

[73] Assignee: **Flamma S.p.A.**, Bergamo, Italy

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/649,620**

[22] PCT Filed: **Jul. 21, 1995**

[86] PCT No.: **PCT/EP95/02897**

§ 371 Date: **May 22, 1996**

§ 102(e) Date: **May 22, 1996**

[87] PCT Pub. No.: **WO96/04240**

PCT Pub. Date: **Feb. 15, 1996**

[30] **Foreign Application Priority Data**

Aug. 4, 1994 [IT] Italy MI94A001693

[51] **Int. Cl.**[6] **C07C 241/00**

[52] **U.S. Cl.** **562/560**

[58] **Field of Search** 562/560

[56] **References Cited**

U.S. PATENT DOCUMENTS

1,967,400	7/1934	Fischl	562/560
4,420,432	12/1983	Chibata	562/560
5,091,171	2/1992	Yu	424/642
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5,627,172	5/1997	Almada	514/120

FOREIGN PATENT DOCUMENTS

0 669 083	8/1995	European Pat. Off. .	
53-6204	3/1978	Japan	562/560
94/02127	2/1994	WIPO .	

OTHER PUBLICATIONS

Chemical Abstracts, vol. 84, No. 1, 1976 Columbus, Ohio, US; p. 13433.

ACTA Physiol. Scand. (1995) , 153 (2), 207–9 Coden: APSCAX: ISSN: 0001–6772, 1995 Earnest, C.P. et al.

Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Griffin, Butler, Whisenhunt & Szipl,

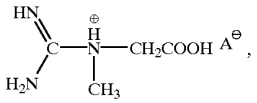
[57] **ABSTRACT**

Hydrosoluble organic salts of creatine are disclosed. The salts are useful in the dietetic and food industry.

3 Claims, No Drawings

HYDROSOLUBLE ORGANIC SALTS OF CREATINE

The present invention refers to hydrosoluble organic salts of creatine of general formula I:



(I)

wherein $A^{\ominus}$ represents the anion of a mono, bi- or tricarboxylic acid. Preferred anions are the citrate, maleate, fumarate, tartrate or malate.

Creatine or N-(aminoiminomethyl)-N-methylglycine is a sarcosine derivative present in the muscle tissue of many vertebrates, man included, mainly combined with phosphoric acid in form of phosphorylcreatine and it is involved in the energy transfer from mitochondria to the ATP utilization sites.

Several studies indicate that there is a relationship between the creatine (phosphoryl creatine) concentration in the muscles having the function of keeping an high intracellular ATP/ADP ratio and maximum sustainable physical effort (Annu. Rev. Biochem. 54: 831–862, 1985; Science 24: 448–452, 1981; BESSMAN S. P., and F. SAVABI. The role of the phosphocreatine energy shuttle in exercise and muscle hypertrophy. In: Biochemistry of Exercise VII. A. W. Taylow, P. D. Gollnick, H. J. Green, C. D. Ianuzzo, E. G. Noble, G. Metivier, and J. R. Sutton., Intl. Series Sports Sciences 21: 167–178, 1990).

The creatine increase in diets may therefore be useful to bring the plasma creatine concentrations at levels providing significant values of creative itself in the muscle. The short creatine half-life in plasma (1–1.5 hours) makes however necessary to reach rapidly said levels and this, in view of the bioavailability degree of creatine, is obtainable only by the administration of high doses of 5–10 g (for mean body weights of 70 kg), amounts well tolerated because of the lack of toxicity of the compound.

The low solubility of creatine in water (1 g in 75 ml) is therefore a practical limitation to the possibility of marking immediately available in the specific diet the necessary amounts of creatine.

WO 94/02127, published on Feb. 3, 1994, discloses the use of creatine, optional combined with aminoacids or other components, in order to increase the muscle performance in mammals.

The present invention provides hydrosoluble stable organic salts of creatine of formula I characterized by high water solubility (from 3 to 15 times higher them that of creatine itself) and a process for their preparation. The salts of formula I are prepared by salifying creatine with the corresponding acids in aqueous or hydroalcoholic concentrated solution or in a water-immiscible solvent, at temperatures ranging from the room temperature to 50° C., optionally concentrating the solutions and filtering the crystallized salts. According to a preferred embodiment the salts of formula I are prepared by reacting creatine with an excess organic acid in ethyl acetate until the salt is completely formed, detectable with the IR analysis, cooling and filtering. The filtrated solvent, containing the excess acid is recycled and, after filling up of the components, is used for a further reaction.

The salts are characterized by IR, melting point, potentiometric and HPLC assay.

Table 1 reports the solubility of the salts I of the invention.

TABLE 1

Creatine salt	Water solubility % (g/100 ml)
Citrate	10
Maleate	19
Fumarate	3
Tartarate	8,5
Malate	4,5

EXAMPLE 1

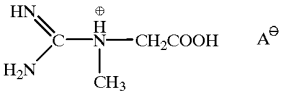
39.45 g (0.18 mol) of monohydrate citric acid are suspended in 100 ml of ethyl acetate. 20 g (0.134 mol) of monohydrate creatine are added to the stirred suspension at 20–25° C. and the mixture is stirred 4 hours at 25° C. After IR control, the product is filtered and washed with ethyl acetate, then dried in oven at 50–55° C., obtaining 90% of salts, m.p. 112–114° C., 99.2% titer.

EXAMPLE 2

14.9 g (0.1 mol) of monohydrate creatine are added to a solution of 11.6 g (0,1 mol) of maleic acid in 20 ml of water. The so obtained solution is concentrated, cooled to 5° C. and the product filtered and dried under vacuum at 50° C., obtaining 87% of salt, m.p. 128–129° C., 99.8% titer.

We claim:

1. An isolated hydrosoluble salt of creatine of the formula:



wherein A^- represents the anion of citric, maleic, fumaric, or malic acid.

2. The hydrosoluble salt of claim **1**, wherein A^- is a citrate anion, said salt having a melting point of 112–114° C.

3. The hydrosoluble salt of claim **1**, wherein A^- is a maleate anion, said salt having a melting point of 128–129° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,973,199

DATED : October 26, 1999

INVENTOR(S) : NEGRISOLI et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page item [75], change "Gianpaolo" to --Giampaolo-- and change "Lucno" to --Lucio--.

Signed and Sealed this

Twenty-eighth Day of March, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Commissioner of Patents and Trademarks

US006716459B2

(12) **United States Patent**
Matsuyama

(10) **Patent No.: US 6,716,459 B2**
(45) **Date of Patent: Apr. 6, 2004**

(54) **COMPOSITION FOR INHIBITING INCREASE OF BLOOD SUGAR LEVEL OR LOWERING BLOOD SUGAR LEVEL**

(76) Inventor: **Futoshi Matsuyama**, c/o Use Techno Corporation, 2101 Osada Ichinotani, Fukuchiyama-shi, Kyoto 620-0848 (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 2 days.

(21) Appl. No.: **10/223,489**

(22) Filed: **Aug. 20, 2002**

(65) **Prior Publication Data**

US 2003/0008025 A1 Jan. 9, 2003

Related U.S. Application Data

(62) Division of application No. 09/437,342, filed on Nov. 10, 1999, now Pat. No. 6,485,760.

(30) **Foreign Application Priority Data**

Dec. 9, 1998 (JP) 10-349667

(51) **Int. Cl.**[7] **A61K 35/78**; A61K 31/015

(52) **U.S. Cl.** **424/774**; 514/693; 514/763; 536/1.11

(58) **Field of Search** 424/774; 514/693, 514/763; 536/1.11

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

JP 07228539 A * 8/1995 ..... A61K/35/78

OTHER PUBLICATIONS

Murakami et al. Screening of plant constituents for effect on glucose transport activity in Ehrlich ascites tumour cells. Chem. Pharm. Bull. (1993) vol. 41 (12), pp. 2129–2131.*

* cited by examiner

Primary Examiner—Marjorie Moran
(74) *Attorney, Agent, or Firm*—Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

A composition for inhibiting an increase in, or lowering, a blood sugar level, which comprises, as a main component, a concentrate of a hot water or alcohol extract of leaves of *Lagerstroemia speciosa*, Linn. or Pers. and has an corosolic acid content of 0.01 to 15 mg per 100 mg of the concentrate, and a method of inhibiting an increase in, or lowering, a blood sugar level by oral administration of the composition.

2 Claims, No Drawings

COMPOSITION FOR INHIBITING INCREASE OF BLOOD SUGAR LEVEL OR LOWERING BLOOD SUGAR LEVEL

CROSS REFERENCE TO RELATED APPLICATION

This application is a divisional of application Ser. No. 09/437,342 filed on Nov. 10, 1999, now U.S. Pat. No. 6,485,760, which claims priority from Japanese Patent Application JP 10-349667 filed on Dec. 9, 1998.

DETAILED DESCRIPTION OF THE INVENTION

1. Field of the Invention

The present invention relates to a composition for inhibiting an increase of a blood sugar level or lowering a blood sugar level. More specifically, it relates to a composition for inhibiting an increase of a blood sugar level or lowering a blood sugar level, which composition contains extract components from *Lagerstroemia Speciosa*, Linn. or Pers. as a main component and has a specific content of corosolic acid.

2. Prior Art of the Invention

Lagerstroemia Speciosa, Linn. or Pers. comes under the loosestrife family of Myrtales and is generally called "queen's crape myrtle" as well, and it occurs widely in south east Asian areas including the Philippines, India, Malaysia, southern China and Australia. In the Philippines in particular, dry leaves and flowers of *Lagerstroemia Speciosa*, Linn. or Pers. are decoted and taken as a drink. This drink is also well known as a folk medicine against diabetes.

Leaves of *Lagerstroemia Speciosa*, Linn. or Pers. have received attention and an extract thereof has been analyzed for obtaining some components. It has been accordingly reported that corosolic acid is contained as one of the components and that the corosolic acid has been studied for its activity by using Ehrlich Ascites Tumour Cells to show that it is a substance which activates the mobility of grape sugar [Chem. Pharm. Bull. 41(12) 2129–2131 (1993)].

The above report is concerned with results of in vitro experiments and merely suggests results of first-stage discrimination test of anti-diabetes activities of corosolic acid.

JP-A-5-310587 discloses an anti-diabetes preparation containing, as an ingredient, a concentrated dry substance (*Lagerstroemia Speciosa*, Linn. or Pres. powder extract) obtained by extracting leaves of *Lagerstroemia Speciosa*, Linn. or Pers. in hot water or an organic solvent. The above preparation is an easily prepared and high-safety anti-diabetes preparation produced by taking out a water-soluble fraction and a lipid-soluble fraction from an extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. and adjusting it to a dry extract. The above publication discloses a preferred embodiment in which the powder extract is diluted, e.g., in a concentration of 2% and taken as a drink, and the anti-diabetes activity thereof is confirmed by an animal experiment using mice diseased with diabetes.

As already described, dry leaves of *Lagerstroemia Speciosa*, Linn. or Pers. have been used as having an effect on the therapy of diabetes in folk medicine. However, it is not clearly known what component(s) of the leaves of *Lagerstroemia Speciosa*, Linn. or Pers. has/have human anti-diabetes activity. It is known that corosolic acid is contained as one component, while the activity thereof is a mere result of a study of the function to activate the mobility of grape sugar in an in vitro experiment using cells.

Further, there has been no specific clinical knowledge of component(s) of the extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. which has/have activity in the therapy of human diabetes. Moreover, there has been found no knowledge obtained by studying a relationship between component(s) of the extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. and an increase in a human blood sugar level.

The present inventor has therefore studied a relationship between component(s) of an extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. and an increase or inhibition of an increase in human blood sugar level on the basis of clinical tests. When a composition which was a concentrated extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. and which had a specific content of corosolic acid was administered to mild-case diabetes patients who had a fasting blood sugar level of slightly higher than approximately 110 mg/dl and who were insulin-non-dependent, it was found that an increase in blood sugar level was inhibited and that the blood sugar levels decreased on average.

According to studies by the present inventors, it has been also found that the composition which had a specific content of corosolic acid can be obtained by extracting, concentration and drying leaves of *Lagerstroemia Speciosa*, Linn. or Pers., under a specific condition.

MEANS TO SOLVE THE PROBLEMS

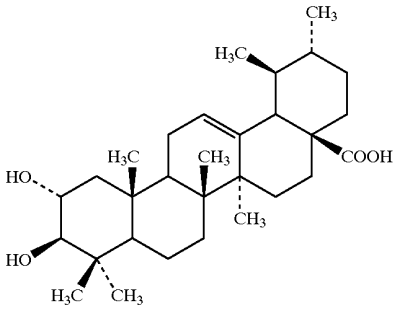
According to the present invention, therefore, there is provided a composition for inhibiting an increase blood sugar level, which comprises, as a main component, a concentrate of a hot water or alcohol extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pres. and has a corosolic acid content of 0.01 to 15 mg per 100 mg of the concentrate.

According to the present invention, further, there is provided a method of inhibiting an increase in a blood sugar level, which comprises orally administering the above composition to a patient who is expected to suffer an increase in blood sugar level from a normal blood sugar level.

Further, according to the present invention, there is provided a method of lowering a blood sugar level to a normal level, which comprises orally administering the above composition to a mild-case diabetes patient having a blood sugar level higher than a normal level to some extent or a serious diabetes patient having a high blood sugar level.

The present invention will be explained more specifically hereinafter.

Corosolic acid is one of triterpenoids having the following structural formula.



It is considered that the activity of the composition of the present invention in inhibiting an increase in, or lowering, a human blood sugar level is caused by the interaction of a

specific content of corosolic acid in the concentrate and extracted components of leaves of *Lagerstroemia Speciosa*, Linn. or Pers.

Leaves of *Lagerstroemia Speciosa*, Linn. or Pers. used as a raw material for the composition of the present invention refer to green leaves of *Lagerstroemia Speciosa*, Linn. or Pers. which occurs in the Philippines or some other areas or a dry product prepared by drying the same. The green leaves may be dried by leaving it in atmosphere, by air-drying or by forcible drying. Preferably, the drying is carried out by so-called toasted-drying until the leaves have a water content of 20% by weight or less, preferably 10% by weight or less, for preventing the growth of microorganisms and attaining storage stability.

Green leaves of *Lagerstroemia Speciosa*, Linn. or Pers. may be extracted as they are, while it is desirable to pulverize the dry leaves or cut them into pieces before the extraction.

The method and condition of extracting leaves of *Lagerstroemia Speciosa*, Linn. or Pers. in hot water or an alcohol and concentrating the extract are not specially limited, while there should be employed a method and a condition under which a resultant concentrate has a specific content of corosolic acid. That is, the concentrate preferably has a corosolic acid content of 0.01 to 15 mg per 100 mg of the concentrate (dry solid substance). The corosolic acid content per 100 mg of the concentrate is preferably 0.1 to 15 mg, more preferably 0.2 to 12 mg, particularly preferably 0.5 to 10 mg.

In the composition of the present invention, those components of the leaves of *Lagerstroemia Speciosa*, Linn. or Pers. which are other than corosolic acid also have an effect on the activity, and it is required to take account of components to be extracted and a concentrating method and condition with regard to other components. A preferred embodiment of a proper method and a proper condition will be apparent from an explanation to be given later.

Method 1

In this method, a pulverization product of dry leaves of *Lagerstroemia Speciosa*, Linn. or Pers. (raw material) added to ethanol or an ethanol aqueous solution (ethanol content 50 to 80% by weight) in an amount 5 to 20 times, preferably 8 to 10 times the weight of the raw material, and the mixture is refluxed under heat at a temperature between room temperature and 90° C., preferably approximately between 50° C. and 80° C., for 30 minutes to 2 hours. The above extraction is repeated twice or three times. The resultant extract may be decolorized as required by adding 5 to 10% by weight, based on the raw material, of activated carbon. The decolorization is useful for expanding the use range of the composition of the present invention to foods, and the like. Then, the extract is filtered and concentrated at a temperature of 60° C. or lower under reduced pressure to obtain a solid, and the solid is dried at a temperature between 50° C. and 70° C. under reduced pressure (higher reduction rate than that during the concentration). The thus-obtained solid is pulverized to obtain a powdery concentrate. The concentrate obtained by the above method has a specific content of corosolic acid and contains an effective amount of other components as well.

Method 2

This method is an extraction method using methanol or a methanol aqueous solution. In this method, the extraction is carried out in methanol or a methanol aqueous solution (methanol content 50 to 90% by weight) in an amount 3 to 20 times the weight of the raw material. The extraction procedure is preferably carried out at a temperature between room temperature and 65° C. for 30 minutes to 2 hours. The number of times of the extraction procedure is not limited to once, and the extraction procedure may be carried out twice or more. The obtained extract is decolorized as required, and concentrated under the same conditions as those in the above method 1, whereby a solid can be obtained.

Method 3

This method 3 is an extraction method using hot water. There is used hot water in an amount 3 to 20 times the weight of the raw material, and the extraction is carried out at a temperature between 50° C. and 90° C., preferably between 60° C. and 85° C., for 30 minutes to 2 hours. Desirably, the concentration and drying after the extraction are carried out for a relatively short period of time since active components may be sometimes deteriorated when the concentrate is maintained at a high temperature for a long period of time. For this reason, it is advantageous to carry out the concentration and the drying under reduced pressure.

The above-explained methods 1 to 3 have been described for explaining basic methods and conditions, and these methods may be altered and/or combined as required. For example, the method 1 and the method 2 may be combined. Of the above methods 1 to 3, the methods 1 and 2 are preferred, and the method 1 is particularly preferred.

Function and Effect of the Composition of the Present Invention

When used as a preparation for inhibiting an increase in, or lowering, the blood sugar level, the composition of the present invention has the following advantages.

(a) It has been reported that conventional oral preparations for the therapy of diabetes such as a sulfonyl urea preparation, a biguanide preparation, an insulin resistant amelioration preparation, etc., causes side effects such as hepatopathy, disorder of digestive organs, nausea, vomitting, etc., while the composition of the present invention is free of these side effects.

(b) The above conventional preparations for the therapy of diabetes end their effects when the administration thereof is discontinued, while the composition of the present invention continues to have an effect and has a continuing effect like traditional Chinese medicine since the blood sugar level does not increase when its administration is discontinued.

(c) The composition of the present invention does not cause a decrease in the blood sugar level when people having a normal blood sugar level takes it.

(d) It is considered that the above advantages of the composition of the present invention are exhibited since corosolic acid contained in leaves of *Lagerstroemia Speciosa*, Linn. or Pers. activates grape sugar transportation even if its concentration is very low.

It is considered that intensification of the grape sugar transportation activity of corosolic acid in "intaking of sugar" and "conversion of sugar to energy" is a function different from that of conventional preparations for the therapy of diabetes.

(e) It is also assumed that the composition of the present invention has another activity in inhibiting the digestion and absorption of glucide by preventing the function of typical digestive enzyme of glucide. It is considered that the above activity is caused by the interaction of corosolic acid and other component(s) in the concentrated extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers.

The composition of the present invention can therefore inhibit an increase in a blood sugar level by orally administering it to patients who are expected to suffer an increase in blood sugar level from a normal blood sugar level. The above oral administration can be continued for a long period

of time, and even if the composition of the present invention is continuedly taken for a long period of time, the blood sugar level comes to be lower than a normal blood sugar level in no case. Further, the oral administration causes no or almost no other harms or side effects.

Further, when orally administered to diabetes patients, the composition of the present invention can lower their blood sugar level to a normal level. The composition of the present invention can work on any one of mild-case patients having a blood sugar level higher than a normal blood sugar level to some extent and serious patients having a considerably higher blood sugar level.

When the composition of the present invention is orally administered, desirably, the dosage of the concentrate having a corosolic acid content of 0.01 to 15 mg per kg of a human body weight per day is 50 mg to 1,000 mg, preferably 70 mg to 800 mg. Specifically, the oral administration is preferably separated to twice or three times a day. Desirably, further, the oral administration of the composition of the present invention is conducted continuedly for at least one month, preferably for at least three months.

The composition of the present invention may have the prepartion form of a powder or granules, and it may also have the preparation form of a tablet such as pellets or an encapsulated preparation.

EXAMPLES

The present invention will be explained more specifically with reference to Examples hereinafter.

Example 1

(1) Preparation of concentrate from dry leaves of *Lagerstroemia Speciosa*, Linn. or Pers.

1 Kg of dry leaves of *Lagerstroemia Speciosa*, Linn. or Pers. from the Philippines were cut, placed in 5 liters of a 80 wt % ethanol aqueous solution and extracted under reflux under heat (approximately 85° C.) for 1.5 hours. After the extraction, the leaves of *Lagerstroemia Speciosa*, Linn. or Pers. were separated by filtration, again placed a 80 wt % ethanol aqueous solution and extracted under reflux under heat (approximately 85° C.) for 1.5 hours. The leaves of *Lagerstroemia Speciosa*, Linn. or Pers. were separated by filtration. Extracts obtained by the first and second extraction procedures were combined, and 500 g of activated carbon was added to carry out decolorization. After the activated carbon was removed, ethanol and water were removed under reduced pressure at 60° C. to give a concentrate. Then, the concentrate was maintained further under reduced pressure at 60° C. to give a dry solid. The solid was pulverized to give 150 g of a powdery concentrate.

(2) Analysis of corosolic acid

One gram of the powder concentrate obtained in the above (1) was dissolved in 10 ml of methanol and analyzed by high-performance liquid chromatography (HPLC) to show a corosolic acid content of 30 mg in the above concentrate (corresponding to 3 mg of corosolic acid per 100 mg of the concentrate).

(3) Preparation of tablet

The powdery concentrate obtained in the above (1) was used to prepare tablets containing the following components for a clinical test.

Components	% by weight
Powdery concentrate	50
Dietary fiber*1	20
Sucrose fatty acid ester	3
Lactose	22
Hardened oil*2	5
	100

*1Crystalline cellulose
*2Hardened rapeseed oil

The above components were homogeneously mixed and prepared into tablets having a weight of 250 mg each ("tablets A" hereinafter) with a tablet machine.

Further, tablets containing no powdery concentrate ("tablets B" hereinafter) which were indistinguishable from the tablets A were prepared in the same manner as above except that diluents alone were used without the powdery concentrate.

(4) Clinical test

Twenty-two mild-case insulin non-dependent patients having a a fasting blood sugar level of approximately 100 to 210 mg/dl were classified into two groups.

The Group I (11 patients of one group) were allowed to take three tablets A each time after meals three times a day with a cup of water for 4 weeks from the beginning of the first to the end of the fourth week, and the tablets B were administered under the same conditions for 4 weeks from the beginning of the fifth week.

On the other hand, the Group II (11 patients of the other group) were allowed to take three tablets B each time after meals three times a day with a cup of water for 4 weeks from the beginning of the first to the end of the fourth week, and the tablets A were administered under the same conditions for 4 weeks from the beginning of the fifth week.

In the beginning of the administration, after 4 weeks and after 8 weeks from the administration, bloods of the patients were sampled three times and studied for blood sugar levels. Table 1 shows the results.

TABLE 1

	Beginning		After 4 weeks		After 8 weeks
Group I (11 patients) Average (mg/dl)	169.1	→ tablet A	132.8	→ tablet B	143.4
Group II (11 patients) Average (mg/dl)	129	→ tablet B	128	→ tablet A	110

The tablets A were studied for a significant difference to show a Prob>(T) value of 0.0030 and that the tablets A had a high-degree significant difference in decreasing the blood sugar level.

What is claimed is:

1. A composition for inhibiting an increase in, or lowering, a blood sugar level, in a human patient in need thereof, consisting essentially of:

a concentrate of ethanol or ethanol aqueous solution extract of leaves of *Lagerstroemia Speciosa*, Linn. or Pers. having a corosolic acid content of 0.01 to 15 mg per 100 mg of the concentrate.

2. The composition according to claim **1**, wherein said ethanol solution contains 50 to 80 by weight of ethanol.

* * * * *

US005968900A

United States Patent [19]

Greenhaff et al.

[11] **Patent Number: 5,968,900**

[45] **Date of Patent: Oct. 19, 1999**

[54] **INCREASING CREATINE AND GLYCOGEN CONCENTRATION IN MUSCLE**

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[73] Assignee: **The University of Nottingham**, Nottingham, United Kingdom

[21] Appl. No.: **08/875,326**

[22] PCT Filed: **Dec. 15, 1995**

[86] PCT No.: **PCT/GB95/02933**

§ 371 Date: **Sep. 29, 1997**

§ 102(e) Date: **Sep. 29, 1997**

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PCT Pub. Date: **Jun. 20, 1996**

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[52] **U.S. Cl.** **514/3**; 514/4; 514/23; 514/53; 514/54; 514/565

[58] **Field of Search** 514/3, 4, 23, 53, 514/54, 565

[56] **References Cited**

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Primary Examiner—Kimberly Jordan

Attorney, Agent, or Firm—Watts, Hoffmann, Fisher & Heinke Co., L.P.A.

[57] **ABSTRACT**

Compositions herein increased creatine retention and/or glycogen storage in muscle. A composition comprises creatine or its derivative and a carbohydrate or its derivative. The carbohydrate is in an amount by weight which is greater than the amount of creatine. The amount of carbohydrate and the amount of creatine are effective for increasing creatine retention and/or glycogen storage in muscle. The compositions may be in the form of a pharmaceutical or a dietary supplement and are intended for use in the human or animal body. Other compositions comprise creatine or an active derivative together with insulin or an active derivative. The amount of creatine and the amount of insulin are effective for increasing creatine retention and/or glycogen storage in muscle. The compositions including creatine and insulin may further contain a carbohydrate or its derivative. A method of increasing creatine retention in a human or animal body comprises causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration. A method of increasing glycogen storage in a human or animal body comprises causing an increase in blood plasma creatine carbohydrate concentration and causing a substantially simultaneous increase in blood plasma creatine concentration. The compositions to increase the creatine retention and/or glycogen storage in the muscle are administered by injection or ingestion.

53 Claims, 3 Drawing Sheets

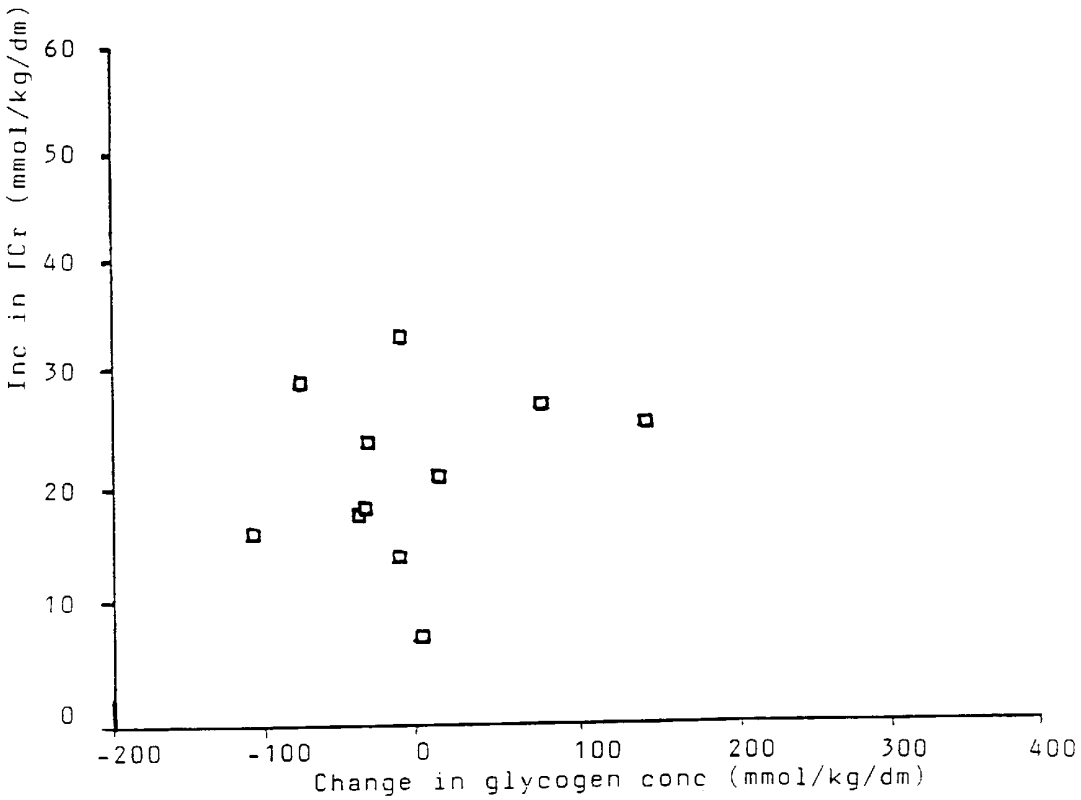

FIGURE 1

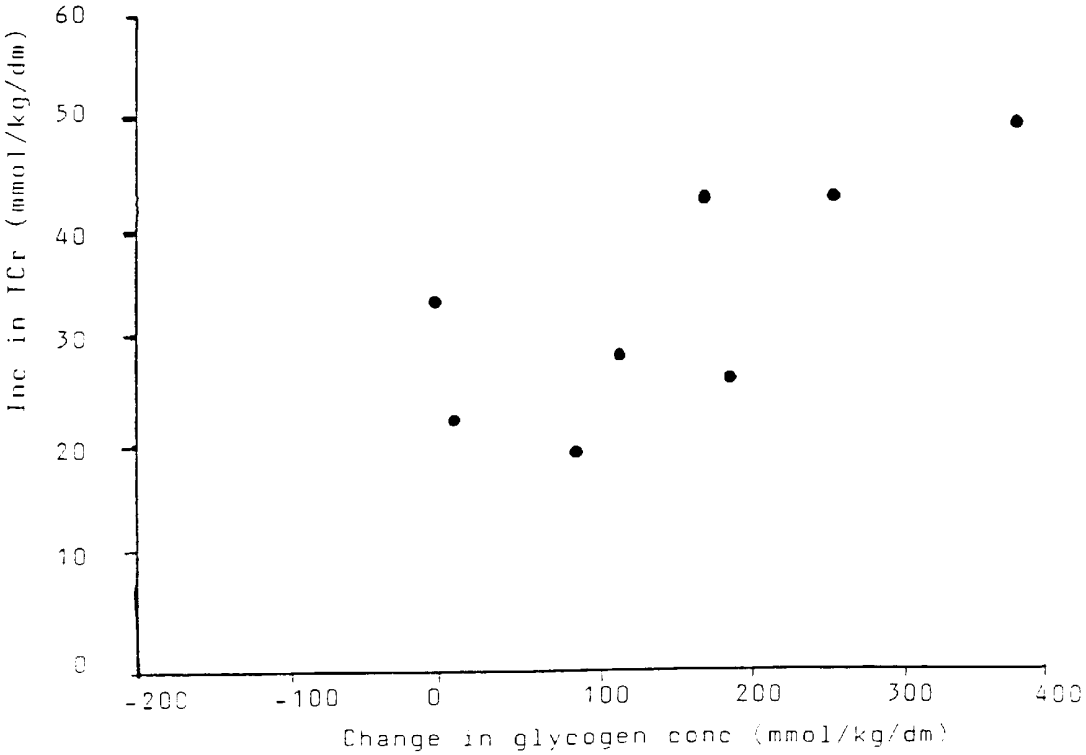

FIGURE 2

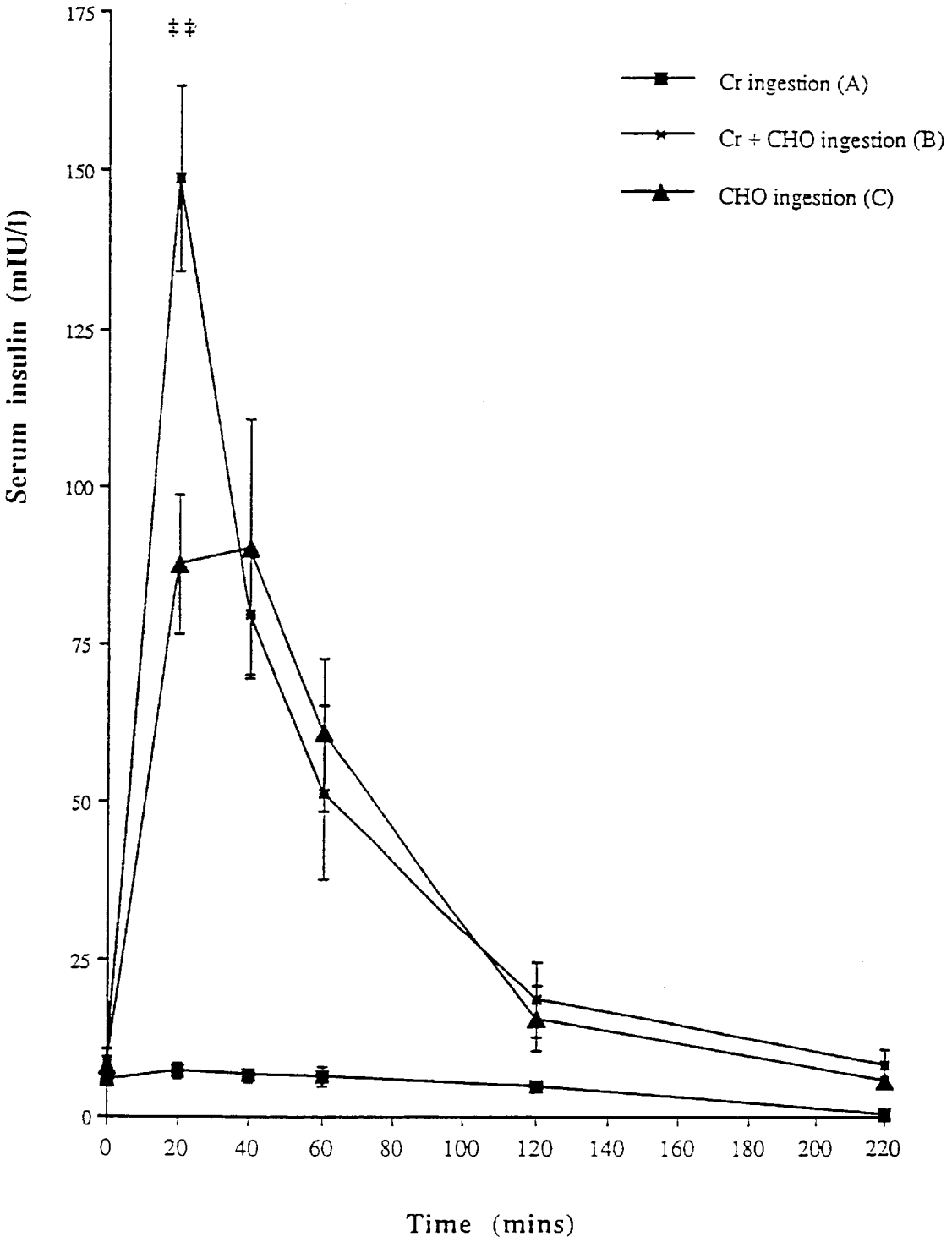
175
150
125
100
75
50
25
0
Serum insulin (mIU/l)
‡‡
Cr ingestion (A)
Cr + CHO ingestion (B)
CHO ingestion (C)
0
20
40
60
80
100
120
140
160
180
200
220
Time (mins)

FIGURE 3

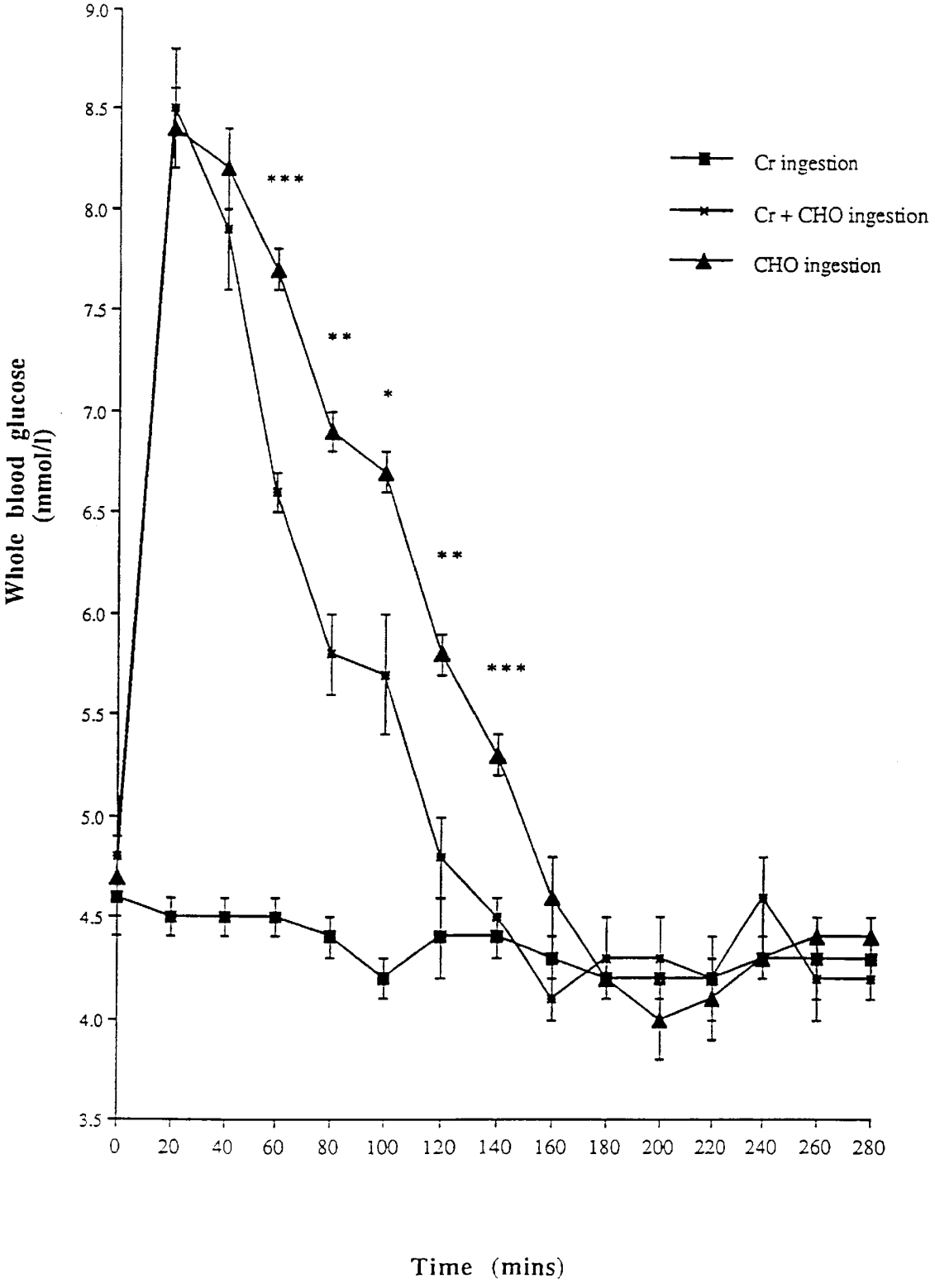
Whole blood glucose (mmol/l)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
***
**
*
**
***
Cr ingestion
Cr + CHO ingestion
CHO ingestion
Time (mins)

FIGURE 4

INCREASING CREATINE AND GLYCOGEN CONCENTRATION IN MUSCLE

This is a 371 of PCT/6B95/02933, filed Dec. 15, 1995.

The present invention concerns the retention of creatine within the body, and relates in particular but not exclusively to a method and composition for increasing creatine uptake in humans. The invention also concerns a method and composition for simultaneously increasing glycogen concentration in muscle.

Creatine (methylglycocyamine, $H_2NC{=}NH{\cdot}N(CH_3)CH_2CO_2H$) is known to be present in the muscles of vertebrates. It is present in a phosphorylated and a non-phosphorylated form and has been shown to be involved in muscular contraction and the development of fatigue. Creatine is produced naturally by the body, but is also obtained from animal foods.

Most bodily creatine is present in muscle, and it is believed that increasing the amount of creatine within muscle favorably affects muscular performance and the amount of work which can be done by the muscle. Accordingly, it is held desirable to be able to influence creatine retention in the body.

Glycogen, $(C_6H_{10}O)x$, is a carbohydrate found in animal cells and is convertible from and to glucose. Athletes endeavour to increase muscle glycogen content before competing in order to enhance muscle performance.

In this specification the term "active derivative" means anything derived from or a precursor of the relevant substance that acts in the same or similar way in the body to the substance, or which is processed into the substance when placed into the body. The terms serum and plasma can be interchanged.

According to the invention there is provided a method of increasing creatine retention in the human or animal body by causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

The plasma creatine concentration may be increased by ingestion and/or in fusion of creatine or an active derivative thereof.

The plasma insulin concentration may be increased by infusion of insulin or an active derivative thereof and/or by the ingestion of an agent operable to cause an increase in the blood plasma insulin concentration.

The agent may be a carbohydrate or an active derivative thereof, preferably a simple carbohydrate. Preferably the carbohydrate is glucose.

Preferably the method comprises the simultaneous ingestion of creatine and an agent operable to cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

The creatine and/or the agent is preferably orally ingested.

The invention further provides a method of increasing glycogen storage, and particularly glycogen concentration in muscle of the human or animal body by causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

The plasma creatine concentration may be increased by ingestion and/or infusion of creatine or an active derivative thereof. The plasma carbohydrate, which is desirably glucose and insulin concentrations may be increased by ingestion of carbohydrate or an active derivative thereof, but desirably glucose and/or any other simple carbohydrate and/or by infusion of a carbohydrate or an active derivative thereof, such as glucose or any other simple carbohydrate.

Preferably creatine or an active derivative thereof and glucose and/or another simple carbohydrate are orally ingested.

According to the invention there is further provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as hereinbefore described. Preferably the composition is ingested in an amount of 100 g to 700 g per day. Which may be taken in four equal parts throughout the day.

Further according to the present invention there is provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

Further according to the present invention there is provided a composition for increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

The composition may be in a form to be ingested and/or injected into the body.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as described above.

According to a further aspect of the invention there is provided a method increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as described above.

Preferably a carbohydrate, or an active derivative thereof, is also ingested and/or injected desirably such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentration.

According to the invention there is also provided a composition for increasing glycogen storage in the animal or human body and particularly glycogen concentration in muscle of the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as hereinbefore described.

Preferably the composition is ingested in an amount of 100 g to 700 g per day, which may be taken in four equal parts throughout the day.

According to the invention there is further provided a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use as an active pharmaceutical composition.

The invention also provides a composition comprising creatine or an active derivative thereof and insulin or an active derivative thereof for use as an active pharmaceutical preparation. The composition may also comprise a carbohydrate or an active derivative thereof.

The invention further provides creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing creatine retention in the human or animal body.

The invention also provides a composition comprising creatine or an active derivative thereof, and insulin or an active derivative thereof, for use in the manufacture of a substance for increasing creatine retention and/or glycogen storage in the human or animal body, such as muscle. Carbohydrate or an active derivative thereof may also be provided.

The invention further provides a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing glycogen concentration in muscle of the human or animal

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

The methods and compositions of the invention may be used to increase bodily creatine retention in humans. This is desired, for example, by sportsmen and athletes to avoid or delay the onset of muscular fatigue. The ability to increase creatine retention may also be desired in individuals having relatively low general creatine levels, for example vegetarians who do not take animal protein, and sufferers of disease which affects muscle. The present invention enables creatine retention to be increased to a greater extent than is achieved by making creatine available to the body alone.

The invention also permits the increase of muscle glycogen concentration. This is desired by athletes to enhance performance. Also, increasing the glycogen concentration in muscle is of interest where insulin sensitivity of the body is impaired by, for example, obesity, diabetes, heart failure or post-surgical trauma.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be further described for the purposes of illustration only with reference to the following examples and to the drawings, in which:

FIG. **1** is a graph showing increase in total creatine concentration against change in glycogen concentration in subjects of group A of Example 2;

FIG. **2** is a similar graph for subjects of group B of Example 2;

FIG. **3** is a graph showing serum insulin concentration against time for all groups in Example 4; and

FIG. **4** is a graph showing blood plasma glucose concentration against time, for all groups in Example 4.

EXAMPLE 1

Experimental

16 men were randomly divided into groups 1 (6 members), 2 (6 members) and 3 (4 members). On day one, fasted subjects gave a blood sample and then consumed the following preparations:

Group 1–5 g creatine in 250 ml low calorie hot orange

Group 2–5 g creatine in 250 ml low calorie hot orange plus 500 ml of a glucose drink (LUCOZADE(™) manufactured by Smith Kline Beecham), containing 90–100 g simple sugars.

Group 3–250 ml of low calorie hot orange

Arterialized-venous blood samples were then obtained at 20 minute intervals for the next 4½ hours, while subjects remained in a supine position. For the remainder of the day, and throughout day two, subjects ingested the mentioned preparations at 4 hourly intervals, representing a total daily creatine dose of 20 g. On the morning of day three the subjects reported back to the laboratory and underwent the same procedures as on the first day. All subjects weighed and recorded their dietary intake throughout the study, subjects in group 2 consuming a prescribed high carbohydrate diet, and undertook 24 hour urine collections on day one and day three. Plasma and urine creatine were measured using high performance liquid chromatography and serum insulin was measured using a radioimmunoassay technique.

Results

The results are shown in Table 1, in which CR=creatine. Plasma creatine concentration (u mol/l) was plotted against time for each group, and the area under each curve was determined. Urinary creatine (g) and peak serum insulin (mIU/l) were also determined.

Plasma creatine concentrations peaked within 90 minutes of creatine ingestion and declined towards resting values during the remaining 180 minutes of the 4½ hour period. The area under the plasma creatine curve was lower in group 2 than in group 1, as was urinary creatine content. Following carbohydrate ingestion, serum insulin levels peaked within 30 minutes in group 2 and returned to the pre-ingestion concentration over the remaining 240 minutes. Plasma insulin concentration did not change in group 1 or group 3 over the course of the experiment.

TABLE 1

	Group 1		Group 2	
	Mean	SE	Mean	SE
		Day 1		
Area under plasma CR (umol/l/min)	2834.1	298.1	883.9^{++}	109.9
Urinary CR (g)	9.5	1.2	5.0*	0.8
Peak serum insulin (mIU/l)	7.8	1.3	72.0^{++}	11.2
		Day 3		
Area under plasma CR (umol/l/min)	2637.5	228.6	948.3*	454.5
Urinary CR (g)	11.9	1.1	5.7^{+}	1.2
Peak serum insulin (mIU/l)	9.5	2.0	84.2^{++}	11.5

*$P < 0.05$; $^{+}P < 0.01$; $^{++}P < 0.001$ - significantly different from corresponding value.

The reduced area under the plasma creatine curve and the lower urinary creatine content of those subjects which had ingested creatine and carbohydrate compared with those

which had ingested only creatine shows that bodily uptake of creatine is greater in the second group. This increase in creatine uptake is believed to be insulin mediated, the plasma insulin concentration being increased by the ingested carbohydrate.

EXAMPLE 2

Experimental

A muscle biopsy sample was taken from the vastus lateralis muscle of each of 21 healthy males and was frozen in liquid nitrogen for subsequent biochemical analysis. Beginning the following day, 12 subjects (group A) each ingested 5 g of creatine dissolved in hot sugar-free orange juice, four times a day for 5 days. The remaining 9 subjects (group B) proceeded as group A, but in addition consumed 500 ml of LUCOZADE, 30 minutes after each creatine preparation had been ingested. Subjects returned the day after the 5th day of supplementation and further muscle biopsy samples were taken. 24 hour urinary collections were made prior to the first biopsy sample (control) and on the first day of creatine supplementation (day 2). Urinary creatine content (in grams) was then measured using high performance liquid chromatography.

Results

Table 2 shows the muscle concentration (mmol/kg dry mass, mean +S.E.M.) of phosphorylated creatine (PCr) non-phosphorylated creatine (Cr) and total creatine (TCr) before and after creatine supplementation. Significant differences between the groups are indicated by an asterisk $p<0.05$.

TABLE 2

	Before Creatine Supplementation	After Creatine Supplementation
	PCr	
Group A	85.1 ± 2.5	92.4 ± 2.1
Group B	84.4 ± 3.8	99.4 ± 2.6*
	Cr	
Group A	36.4 ± 1.7	49.8 ± 1.5
Group B	39.0 ± 2.3	57.1 ± 3.4*
	TCr	
Group A	121.5 ± 3.1	142.2 ± 2.6
Group B	123.4 ± 4.3	156.4 ± 5.4*

The increase in total creatine concentration after supplementation in group B was approximately 60% greater than that in group A. This increase comprises increases in both phosphorylated and non-phosphorylated creatine. Urinary creatine content was greater in group A than in group B on day 2 but there was no difference between the groups on the control day.

These results indicate that carbohydrate ingestion increases uptake of creatine in muscle in man, and to a far greater extent than to that seen when creatine alone is ingested.

EXAMPLE 3

The muscle samples obtained in the study of Example 2 were additionally analysed for muscle glycogen concentration. Muscle samples from a further group C containing 8 subjects were also analysed. This group has followed a similar regime to groups. A and B but ingested a preparation of carbohydrate but no creatine, in the form of 500 ml LUCOZADE, at same times as subjects of Groups A and B.

Table 3 shows the muscle concentration (mmol/kg) of glycogen before and after supplementation, and also the difference in the concentration.

TABLE 3

	before supplementation	after supplementation	difference
Group A			
mean	364.8	366.1	1.2
sd	63.4	65.8	67.9
se	19.1	19.8	20.5
Group B			
mean	331.1	488.7	157.6
sd	32.5	125.4	126.8
se	10.8	41.8	42.3
Group C			
mean	337.5	413.3	75.8
sd	37.3	55.9	33.2
se	13.2	19.8	11.7

sd = standard deviation, se = standard error

Table 3 shows that the mean glycogen difference after supplementation in Group A, who took creatine only, was very small.

The subjects of Group C, who took glucose only, showed an increase in muscle glycogen concentration after supplementation. However, a more marked increase in muscle glycogen concentration was shown by Group B, who took creatine and glucose together. The results of individual subjects in Group B varied greatly. However, referring to FIG. **2** it is shown that there was a linear relationship between the increase in creatine concentration and the increase in glycogen concentration in subjects of this group, showing a synergistic effect. No such relationship was observed in the subjects in Group A, who ingested only creatine (FIG. **1**).

EXAMPLE 4

Experimental

Twenty nine fasted subjects were divided randomly into three groups, group A (12 subjects), group B (9 subjects) and group C (8 subjects). Each member of group A ingested 5 g of creatine dissolved in hot sugar-free orange juice. Each member of group B ingested 5 g of creatine dissolved in hot sugar-free orange juice along with 500 ml of LUCOZADE, 30 minutes after the creatine preparation had been ingested. Group C ingested 500ml of LUCOZADE alone.

Arterialised-venous blood samples were obtained from each member of each group before ingestion and at 20 minute intervals immediately following ingestion for the following 220 minutes, while subjects remained in a supine position. Blood serum insulin concentration was measured in each sample, and the results are shown in Table 4 below. Serum insulin concentration (mIU/l) was plotted against time (mins) for each group and is shown in FIG. **3**.

The whole blood glucose concentration was also measured before ingestion and at 20 minute intervals for the following 280 minutes and the results obtained are shown in Table 5 below. Whole blood glucose (mmol/l) was plotted against time (mins) for each group and is shown in FIG. **4**.

TABLE 4

Gp	Time (min)	Plasma Insulin (mIU/l, mean ± SEM) 0	20	40	60	120	220
A	Creatine	5.8 ± 0.8	7.3 ± 1.2	6.5 ± 1.0	6.3 ± 1.6	4.7 ± 0.3	4.7 ± 0.4
B	Creatine + carbohydrate	8.8 ± 2.0	148.7 ± 14.7	79.7 ± 9.3	51.5 ± 13.7	18.6 ± 6.0	8.2 ± 2.4
C	Carbohydrate	8.0 ± 1.5	87.6 ± 11.1	90.2 ± 20.4	60.8 ± 12.1	15.6 ± 5.2	5.8 ± 0.5

TABLE 5

Gp	Time (min)	Plasma Glucose (mmol/l, mean ± SEM) 0	20	40	60	80	100
A	Creatine	4.6 ± 0.2	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	4.2 ± 0.1
B	Creatine + carbohydrate	4.8 ± 0.2	8.5 ± 0.3	7.9 ± 0.2	6.6 ± 0.1	5.8 ± 0.5	5.7 ± 0.3
C	Carbohydrate	4.7 ± 0.2	8.4 ± 0.2	8.2 ± 0.2	7.7 ± 0.1	6.9 ± 0.0	6.7 ± 0.1

Gp	Time (min)	120	140	160	180	200	220	240	280
A	Creatine	4.4 ± 0.2	4.4 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.2	4.3 ± 0.1	4.3 ± 0.1
B	Creatine + carbohydrate	4.8 ± 0.2	4.5 ± 0.1	4.1 ± 0.1	4.3 ± 0.2	4.3 ± 0.2	4.2 ± 0.2	4.6 ± 0.2	4.2 ± 0.1
C	Carbohydrate	5.8 ± 0.1	5.3 ± 0.3	4.6 ± 0.2	4.2 ± 0.1	4.0 ± 0.2	4.1 ± 0.2	4.3 ± 0.1	4.4 ± 0.1

The results shown in Table 4 and FIG. **3** clearly show that when creatine is ingested along with carbohydrate (group B), the serum insulin concentration is considerably greater than that found when creatine (group A) and carbohydrate (group C) are ingested alone.

Further, the results shown in Table 5 and FIG. **4**, clearly show that when creatine and carbohydrate (group B) are ingested together, there is a considerably more rapid decline in blood plasma glucose concentration, than when carbohydrate is ingested alone. This is a direct result of the augmented release of insulin into the blood caused by the ingested creatine and glucose composition.

This rapid decline in blood plasma glucose concentration is indicative of an increased uptake of glucose into muscle for glycogen synthesis (as seen in Example 3). In other words, the ingestion, or infusion, of creatine in conjunction with carbohydrate increases muscle glycogen storage.

Modifications may be made within the scope of the invention. In particular the carbohydrate may be varied. for example by the use of another simple carbohydrate such as a di-or trisaccharide, although glucose is preferred because of the rapidity with which it enters the bloodstream after ingestion, causing substantially simultaneous peaks in blood insulin and creatine concentrations, and to maximise plasma insulin increase. The creatine, glucose and/or insulin or active derivatives of any of these may be infused into the blood in any suitable manner, for example by injection.

Further, the carbohydrate may be substituted or accompanied by insulin or an active derivative thereof. Ingestion or injection of compositions comprising creatine (or an active derivative thereof) and insulin (or an active derivative thereof) may be complimented by ingestion of carbohydrate, such as glucose, for example in the form of a drink. The timing of ingestion or injection (infusion) of the composition and carbohydrate is such that the increase in blood plasma carbohydrate concentration and insulin concentration and plasma creatine concentration peak substantially simultaneously.

Whilst endeavouring in the foregoing Specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

What is claimed is:

1. A method of increasing creatine retention in a human or animal body comprising causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

2. The method according to claim **1** comprising increasing the plasma creatine concentration by ingestion of creatine or an active derivative thereof.

3. The method according to claim **1** comprising increasing the plasma creatine concentration by infusion of creatine or an active derivative thereof.

4. The method according to claim **1** comprising increasing the plasma insulin concentration by infusion of insulin or an active derivative thereof.

5. The method according to claim **1** comprising increasing the plasma insulin concentration by ingestion of an agent operable to cause an increase in the blood plasma insulin concentration.

6. The method according to claim **5** wherein the agent is a carbohydrate or an active derivative thereof.

7. The method according to claim **5** wherein the agent is a simple carbohydrate.

8. The method according to claim **7** wherein the simple carbohydrate is glucose.

9. The method according to claim **5** wherein at least one of the creatine and the agent is orally ingested.

10. The method according to claim **1** comprising increasing the blood plasma creatine concentration by administering creatine or an active derivative thereof and increasing the blood plasma insulin concentration by administering a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

11. The method according to claim **10** wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

12. The method according to claim 1 comprising ingesting creatine and an agent operable to cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

13. A method of increasing glycogen storage in a human or animal body comprising causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

14. The method according to claim 13 comprising increasing the plasma creatine concentration by administering creatine or an active derivative thereof by at least one of ingestion and infusion.

15. The method according to claim 13 comprising increasing the plasma carbohydrate and insulin concentrations by administering a carbohydrate or an active derivative thereof by at least one of ingestion and infusion.

16. The method according to claim 13 comprising increasing the plasma glucose and insulin concentrations by infusion of a carbohydrate or an active derivative thereof, the carbohydrate being selected from the group consisting of glucose and other simple carbohydrates.

17. The method according to claim 13 comprising orally ingesting creatine or an active derivative thereof and a carbohydrate or an active derivative thereof, the carbohydrate being selected from the group consisting of glucose and other simple carbohydrates.

18. The method according to claim 13 comprising increasing the blood plasma creatine concentration by administering creatine or an active derivative thereof and increasing the blood plasma insulin concentration by administering a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

19. The method according to claim 18 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

20. A composition for use in a human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase creatine retention in the body.

21. The composition according to claim 20 wherein the composition is in the nature of a dietary supplement.

22. The composition according to claim 20 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

23. The composition according to claim 20 wherein the composition comprises in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

24. The composition according to claim 20 wherein the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase glycogen storage in the body.

25. A method of increasing creatine retention in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof by at least one of ingestion and injection, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

26. The method according to claim 25 wherein the composition is ingested in an amount of 100 g to 700 g per day.

27. The method according to claim 25 wherein the composition is administered in four equal parts throughout the day.

28. The method according to claim 25 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

29. The method of claim 25 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

30. A composition for use in a human or animal body comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

31. The composition according to claim 30 wherein the creatine or its derivative and the insulin or its derivative are present in amounts effective to increase glycogen storage in the body.

32. The composition according to claim 30 wherein the creatine or its derivative and the insulin or its derivative are present in amounts effective to increase creatine retention in the body.

33. The composition according to claim 30 wherein the composition is in a form that can be administered by at least one of ingestion and injection.

34. 8 The composition according to claim 30 further comprising a carbohydrate or an active derivative thereof.

35. A method of increasing creatine retention in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof by at least one of ingestion and injection.

36. A method according to claim 35 further comprising administering a carbohydrate or an active derivative thereof such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentration.

37. A method of increasing glycogen storage in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof by at least one of ingestion and injection.

38. A method according to claim 37 further comprising administering a carbohydrate or an active derivative thereof such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentrations.

39. A method of increasing glycogen storage in the human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof by at least one of ingestion and infusion, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

40. A method according to claim 39 wherein the composition is ingested in an amount of 100 g to 700 g per day.

41. A method according to claim **39** wherein the composition is administered in four equal parts throughout the day.

42. The method according to claim **39** wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

43. The method according to claim **39** wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

44. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in the amount by weight which is greater than an amount of the creatine or its derivative, and the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase creatine retention in the body.

45. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

46. The pharmaceutical according to claim **45** wherein the composition further comprises a carbohydrate or an active derivative thereof in an amount by weight which is greater than an amount of the creatine or its derivative.

47. A composition for use in a human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase glycogen storage in the body.

48. The composition according to claim **47** wherein the composition is in the nature of a dietary supplement.

49. The composition according to claim **47** wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

50. The composition according to claim **47**, wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative in an amount ranging from 92 to 98%.

51. The composition according to claim **47** wherein the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase creatine retention in the body.

52. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase glycogen storage in the body.

53. A composition for use in a human or animal body comprises, in % by weight based upon a total weight of the composition: creatine or its derivative present in an amount ranging from 2 to 8% and a carbohydrate or its derivative in an amount ranging from 92 to 98%.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 5,968,900

DATED: October 19, 1999

INVENTOR(S): Paul Leonard Greenhaff

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item

[30] **Foreign Application Priority Data**

Aug. 17, 1994 [GB] United Kingdom.....9425514.8

Signed and Sealed this

Twelfth Day of September, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Director of Patents and Trademarks

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

IOVATE HEALTH SCIENCES U.S.A., INC., IOVATE HEALTH SCIENCES INTERNATIONAL, INC., IOVATE T & P, INC., FLAMMA SpA, and USE TECHNO CORPORATION,

(b) County Of Residence Of First Listed Plaintiff: (Except In U.S. Plaintiff Cases)

DEFENDANTS

WELLNX LIFE SCIENCES INC (d/b/a NV Inc.), NXCARE INC., NXLABS INC., SLIMQUICK LABORATORIES, BIOGENETIX, DEREK WOODGATE, and BRADLEY WOODGATE,

County Of Residence Of First Listed Defendant: (IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED

(c) Attorneys (Firm Name, Address, And Telephone Number)
Josy W. Ingersoll, Esquire (#1088)
John W. Shaw, Esquire (#3362)
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P.O. Box 391
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(302) 571-6672

Attorneys (If Known)

II. BASIS OF JURISDICTION (PLACE AN X IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place An X In One Box For Plaintiff And One Box For Defendant) (For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in This State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

V. NATURE OF SUIT (Place An X In One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL ROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence Habeas Corpus
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 U.S.C. 881
- ☐ 630 Liquor Laws
- ☐ 640 R R & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt Relations
- ☐ 730 Labor/Mgmt. Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl Ret Inc Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 U.S.C. 158
- ☐ 423 Withdrawal 28 U.S.C. 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 U.S.C. 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates, etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 U.S.C. 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

IV. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding ☐ 2 Removed from Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

(CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY.):
35 U.S.C. § 1 et seq. and 28 U.S.C. §§ 1331 and 1338.

Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 ☐ YES ☐ NO **DEMAND $**

Check YES only if demanded in complaint
JURY DEMAND: ☐YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See instructions) JUDGE: DOCKET NUMBERS:

DATE 5/24/07 SIGNATURE OF ATTORNEY OF RECORD Karen E. Keller #4489

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs - Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved).

(c) Attorneys. Enter firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)."

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction is based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause.

V. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

VI. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C. Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate's decision.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS-44 is used to reference relating pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 07-286

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 7 COPIES OF AO FORM 85.

MAY 21 2007
(Date forms issued)

Shane Handlin
(Signature of Party or their Representative)

Shane Handlin
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action